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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte AGATHE SUBTIL,
CLAUDE PARSOT, and ALICE DAUTRY-VARSAT

Appeal 2009-002931[1]
Application 10/014,670
Technology Center 1600

Decided: October 26, 2009

Before LORA M. GREEN, RICHARD M. LEBOVITZ, and FRANCISCO C. PRATS, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on the appeal by patent applicants from the patent examiner's rejection of claims 7-10, 34-37, and 44-47. Jurisdiction for this appeal is under 35 U.S.C. § 6(b). We affirm.

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[1] Heard Sep. 17, 2009.

STATEMENT OF THE CASE

The claims are directed to methods of expressing and secreting *Chlamydia* polypeptides in gram-negative bacteria strains containing a type III secretion pathway. Chlamydiae are gram-negative bacteria that proliferate only within eukaryotic host cells, causing diseases such as pneumonia and pelvic inflammatory disease (Spec. 1). The type III secretion machinery facilitates the translocation of *Chlamydia* proteins into the host cell's cytoplasm where the bacteria reside (*id.* at 5).

Claims 7-10, 34-37, and 44-47 are appealed and stand rejected by the Examiner as follows:

Claims 7-10, 34-37, and 44-47 under 35 U.S.C. § 103(a) as obvious in view of Griffais et al. (US 6,559,294 B1, issued May 6, 2003), Demers et al. (WO 99/58714, published Nov. 18, 1999), and Kalman et al. (Comparative genomes of *Chlamydia pneumoniae* and *C. trachomatis*, 21 NATURE GENETICS 385-389 (1999)) (Ans. 3); and

Claims 7-10, 34-37, and 44-47 under 35 U.S.C. § 103(a) as obvious in view of Stephens et al. (US 6,822,071 B1, issued Nov. 23, 2004) and Demers (Ans. 6).

Claims 7, 8, and 9 are representative and read as follows:

> 7. A method for identifying a secreted *Chlamydia* polypeptide wherein said method comprises (a) providing a recombinant expression vector containing at least DNA coding for the polypeptide of interest; (b) transforming a Gram-negative strain containing a type III secretion pathway with said recombinant vector; (c) expressing said vector in said Gram-negative transformed strain; and (d) detecting the secretion of said DNA expression product; wherein the secretion of said expression product indicates that it corresponds to a secreted *Chlamydia* polypeptide.

8. A method for identifying a secreted Chlamydia polypeptide wherein said method comprises (a) providing a recombinant expression vector containing at least DNA coding for the polypeptide of interest fused to a reporter gene; (b) transforming a Gram-negative strain containing a type III secretion pathway with said recombinant vector; (c) expressing this vector in said transformed Gram-negative strain; and (d) detecting the secretion of said reporter gene expression product; wherein the secretion of said expression product indicates that the fused DNA contains at least a polynucleotide corresponding to a secreted *Chlamydia* polypeptide.

9. A method according to Claims 7 or 8 wherein said Gram-negative strain containing a type III secretion pathway is a *Shigella* strain.

THE CLAIMS

1. Claim 7 is to a method "for identifying a secreted *Chlamydia* polypeptide" comprising four steps:

2. (a) providing an expression vector containing a DNA coding for a polypeptide of interest;

3. (b) transforming a "Gram-negative strain containing a type III secretion pathway" with the vector;

4. (c) expressing the vector in the Gram-negative strain; and

5. (d) detecting secretion of the DNA "wherein the secretion of said expression product indicates that it corresponds to a secreted *Chlamydia* polypeptide."

6. Claim 8 is to a similar four step method as in claim 7, but the (a) DNA coding for a polypeptide of interest is "fused to a reporter gene."

7. Claim 9 is to the method of claim 7 or 8 in which the gram-negative strain "is a *Shigella* strain."

OBVIOUSNESS – GRIFFAIS, DEMERS, & KALMAN

Claims 7-10, 34-37, and 44-47 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Griffais, Demers, and Kalman (Ans. 3).

Facts

Demers

8. "Type III secretion machinery is present in numerous gram-negative bacteria (including members of the species *Shigella*, *Salmonella*, *Yersinia*, *Escherichia*, *Pseudomonas*, *Xanthomonas*, *Ralstonia*, and *Erwinia*)" (1:11-13).

9. Demers describes methods of identifying molecules which activate or inhibit secretion in wild-type strains of gram-negative bacteria (3:1-3).

10. The methods involve expressing a reporter gene fused to a promoter of a gene regulated by type III secretion machinery in wild-type gram-negative bacteria and "mutants of these bacteria that constitutively secrete proteins via the type III secretion machinery or are deficient for secretion" (3:4-13).

11. The presence or activity of the reporter gene "can be used as an indicator of the secretion activity of the type III secretion machinery" (3:13-16).

12. Demers states that "[a]ny gram-negative bacterial containing type III secretion machinery may be used in the methods" (3:23-26), and describes specific examples using *Shigella* (6:1-3).

13. Demers describes the detection of 15 proteins secreted by *Shigella* in its model system (7:2-25).

Griffais

14. Griffais describes host cells transformed with a vector comprising *Chlamydia* nucleotide sequences, and the expression and secretion of the polypeptides encoded by the sequences (col. 1, ll. 15-22; col. 48, ll. 25-65; col. 50, ll. 41-51).

15. The secreted polypeptides include type III secreted polypeptides which "may be detected by techniques known to persons skilled in the art, such as for example the techniques using cloning combined with vectors allowing the expression of the said polypeptides fused to export markers such as the luc gene for luciferase or the PhoA gene for alkaline phosphatase." (Col. 40, ll. 20-27.)

16. The "vectors comprise the elements necessary to allow the expression and/or the secretion of the said nucleotide sequences in a given host cell" and may include "particular signals specifying the secretion of the translated protein" (col. 46, ll. 14-23).

17. "[P]referred" host cells are gram-negative bacteria and "a bacterium belonging to the Chlamydia family" (col. 48, ll. 59-64).

Kalman

18. Kalman describes various *Chlamydia* polypeptides, including type III secreted polypeptides (p. 385, col. 2).

Differences between the claimed invention and the prior art

19. As found by the Examiner, Griffais taught the expression vector, transformation of a gram-negative host with the vector, expression of the

vector, and the detecting steps recited in steps (a) through (d) of claims 7 and 8 method (F14-F17; Ans. 4).

20. The secreted polypeptides described in Griffais were *Chlamydia* polypeptides (F14) as in the claims.

21. Griffais also disclosed that the *Chlamydia* polypeptide could be fused to an "export marker" (F15) which served the same purpose as the "reporter gene" of claim 8. Demers also taught the use of a reporter gene to indicate secretion activity of type III secretion machinery (F10-11).

22. The Examiner found that Griffais did not describe utilizing a *Shigella* host as recited in claim 9, but found that Demers taught such an expression host (F12) in a similar expression method, and concluded that it would have been obvious to have used it as a "known technique" to "yield predictable results." (Ans. 4 & 10-11.)

Level of ordinary skill in the art

23. Based on the teachings of Demers (F12-13) and Griffais (F17), persons of ordinary skill in the art would have believed it reasonably predictable that *Chlamydia* polypeptides would be successfully secreted in other gram-negative bacteria, including *Shigella*.

Statement of Issue

Appellants contend that the Examiner erred for two reasons (App. Br. 6):

• Persons of ordinary skill in the art would not have used Demers' secretion system because Demers' "entire disclosure is directed to looking

for agents that block secretion or change expression patterns NOT for determining whether a certain Chlamydia protein is one that can be secreted through the type III pathway." (App. Br. 7.)

• The "cited art provides no reason to believe that the expression of Chlamydia proteins would, in fact, work in other gram negative strains such as Shigella." (App. Br. 7.)

Therefore, the issues in this rejection are whether Appellants established that the Examiner erred in combining Demers with Griffais and, in doing so, also erred in concluding that there was a reasonable expectation of success.

Principles of Law

An obviousness "analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

In assessing a claim's obviousness, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416.

Analysis

Appellants contend that the Examiner erred in combining Demers with Griffais because the purpose of Demers was to identify agents that blocked secretion, not to determine whether a *Chlamydia* polypeptide could be secreted by a type III pathway. This argument does not persuade us that the Examiner erred.

First, the Examiner relied upon Demers for its teaching that various gram-negative hosts, including *Shigella*, could be used for secreting a type III polypeptide. Thus, even were the methods to differ between Griffais and Demers, the Examiner did not solely rely on Demers for meeting the limitations of steps (a) through (d) of claims 7 and 8.

Secondly, Demers describes steps of expressing and detecting type III polypeptides in gram-negative bacteria (F10-13) as in claims 7 and 8, and therefore was properly combined with Griffais, which was directed to the same type of expression methods. As both references are in the same field of endeavor, persons of ordinary skill in the art would have found them pertinent to the problem addressed by the claim of expressing polypeptides in hosts with type III expression machinery.

Finally, the claimed method recites "comprising" which is open-ended language that does not exclude additional steps, including a step of identifying molecules that regulate secretion in gram-negative bacteria as in the Demers publication (F9). Consequently, Appellants' argument that Demers' purpose is different from the claimed invention is not persuasive because the claims do not exclude Demers' molecule identification method.

Appellants also assert that the inventors' discovery that *Chlamydia* proteins could be expressed and secreted in *Shigella* would not have been predicted by the prior art (App. Br. 7). They assert that the protein sequences utilized in the *Chlamydia* secretion machinery are not conserved as compared to other gram-negative bacteria and therefore the secretion signals would differ (*id.*). They also cited the abstracts of several publications which they contend demonstrate that other proteins, such as chaperone proteins, are needed to achieve secretion in gram-negative bacteria (*id.* at 8).

Appellants have not provided adequate evidence that persons of skill in the art would have viewed expression of a *Chlamydia* polypeptide in other gram-negative host as unpredictable. Attorney argument is not evidence. *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). Nor can it take the place of evidence lacking in the record. *Meitzner v. Mindick*, 549 F.2d 775, 782 (CCPA 1977). For example, Appellants did not provide evidence that the secretion signals in a *Chlamydia* protein would not be recognized in *Shigella* or other gram-negative bacteria.

The Examiner, on the other hand, introduced Demers' teaching that any gram-negative bacteria containing type III secretion machinery could be utilized in its expression methods (F12-13) and the Griffais statement that gram-negative bacteria were preferred hosts for *Chlamydia* polypeptide secretion (F17), evidencing that persons of ordinary skill in the art believed it predictable that a *Chlamydia* polypeptide could be secreted in gram-negative hosts, including *Shigella*.

As to the presence of chaperones,[2] the Parsot abstract establishes that chaperones are involved in the type III secretion pathway of gram-negative bacteria; the Tucker abstract describes chaperones in *Salmonella*; and the Fields and Slepenkin abstracts relate to chaperones in *Chlamydia* (App. Br. 8). Appellants have not explained how the presence of chaperones in gram-negative bacteria, including *Chlamydia*, would make expression in gram-negative hosts unpredictable. To the contrary, the abstracts provide further evidence of the similarities in type III secretion pathways in gram-negative bacteria, further buttressing the evidence of predictability provided by Demers and Griffais (F23).

For the forementioned reasons, we conclude that Appellants did not establish that the Examiner erred in reaching the conclusion that the claimed subject matter would have been obvious persons of ordinary skill in the art.

OBVIOUSNESS – STEPHENS AND DEMERS

Claims 7-10, 34-37, and 44-47 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Stephens and Demers (Ans. 6).

Facts

Stephens

24. Stephens describes expression of nucleic acids coding for secreted *Chlamydia* polypeptides in host cells using "routine techniques" and

[2] Appellants cited abstracts of articles by Parsot, Tuckerdagger et al., Fields et al. and Slepenkin et al. (App. Br. 8).

purifying the secreted polypeptide (col. 15, ll. 25-33 & 40-43; col. 16, ll. 4-15 & 42-44).

25. Stephens states that well-known cells and cell lines, such as *E. coli*, can be used as hosts to express the *Chlamydia* polypeptides (col. 16, ll. 16-20).

Differences between the claimed invention and the prior art

26. Stephens, as found by the Examiner and supported by the evidence, describes "a method of identifying a secreted *Chlamydia polypeptide* comprising using a vector and transforming the cells into host cells (columns 15 and 16)," expression in *Escherichia coli* which is a gram negative bacteria (F8), and identifying the secreted polypeptide (Ans. 6; F24-25) as in claims 7 and 8.

27. The Examiner found that Stephens does not "teach the claim limitation 'wherein said gram-negative strain containing a type III secretion pathway is a *Shigella* strain," but concluded that it would have been obvious to the skilled worker because Demers teaches "that gram-negative bacteria contain type III secretion machinery and can secrete proteins via this machinery (pages 1 and 2). Demers et al teach that *Shigella* species can be used to secrete proteins (pages 1 and 6-9)." (App. Br. 7.) The Examiner's finding is supported by the evidence.

Level of ordinary skill in the art

28. Based on the teachings described in Stephens (F24-25) and Demers (F12-13), persons of ordinary skill in the art would have believed it reasonably predictable that *Chlamydia* polypeptides would be successfully secreted in other gram-negative bacteria, including *Shigella* (*see* App. Br. 7).

Statement of the Issue

Appellants contend that neither "Stephens nor Demers describes a method for identifying secreted proteins but rather the general methodology for expressing proteins (which is even acknowledged by Stephens in column 15)" and that therefore the combined references fail to teach or suggest the claimed invention (App. Br. 9). Appellants also contend that "it is known that the proteins which make the Chlamydia secretion machinery are not well conserved compared" to those of other bacteria" (*id.* at 10).

The issues are therefore whether Appellants have established that the Examiner erred in finding that Stephens and Demers suggested all the steps of the claimed method and whether persons of ordinary skill in the art would have reasonably expected *Chlamydia* polypeptides to be expressed in gram negative bacteria, such as *Shigella*.

Analysis

The Examiner's findings that Stephens describes steps (a) through (d) of claim 7 and 8 are supported by factual findings (*see* F24-26; Ans. 6). Appellants have not identified any specific error in these findings nor do we find one. As to Appellants' argument that it would have been unpredictable

that a *Chlamydia* polypeptide would be secreted by other gram-negative bacteria, such as *Shigella*, Appellants have not presented any countervailing evidence or reason to doubt the statements in Stephens (F25) and Demers (F12-13) that any gram-negative host would be suitable to secrete a *Chlamydia* polypeptide. The Examiner's position that persons of ordinary skill in the art would have reasonably believed it predictable that *Chlamydia* polypeptides would be successfully secreted in other gram-negative bacteria, including *Shigella* (F28) is fact-based and supported by the evidence.

CONCLUSIONS OF LAW & SUMMARY

The Examiner did not err in finding all the limitations of claims 7 and 8 to have been taught or suggested by the prior art. The Examiner did not err in concluding that the ordinary skilled worker would have reasonably believed that a *Chlamydia* polypeptide would be successfully secreted in gram-negative bacteria, including *Shigella* as recited in claim 9. The obviousness rejections of claims 7-9 are affirmed.

Claims 10, 34-37, and 44-47 fall with claims 7-9 because separate reasons for their patentability were not provided. See 37 C.F.R. § 41.37(c)(1)(vii).

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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